L6 ANSWER 3 OF 4 USPATFULL

SUMM . . . as seen in periodontium (Sorsa et al., Infect. Immun. 1992, 60:
4491-4495). Recent studies indicate that a serine protease, i.e., **elastase**, may play a role in connective tissue breakdown and tissue invasion in the Dunning rat model of cancer invasion and. . .

SUMM . . . cartilage degradation (Greenwald et al., Bone 1998, 22:33-38; Ryan et al., Curr. Op. Rheumatol. 1996, 8;238-247). MMP-20 is expressed by **oral** squamous cell carcinoma cells (Salo et al., J. Dent. Res. 1998, 77:829, Abstr. No. 1978). Bourguignon et al. (Mol. Biol.. . .

SUMM . . . deficiency syndrome (AIDS), burns, wounds such as bed sores and
varicose ulcers, fractures, trauma, gastric ulceration, skin diseases such as **acne** and psoriasis, lichenoid lesions, epidermolysis bullosa, aphthae (reactive **oral** ulcer), dental diseases such as periodontal diseases, peri-implantitis, jaw cysts and other periapical cysts, dental conditions which are the target of root canal treatment or endodontic treatment, related diseases, **external** and intrinsic root resorption, caries etc.

SUMM The serine proteinases include human leukocyte **elastase** (HLE) and cathepsin G, and additional serine proteinases are involved in the cascade of pathways involved in connective tissue breakdown. . .

SUMM MMP's and serine proteinases can work in **combinations** to bring about destruction of most of the elements of the extracellular matrix and basement membranes. As examples of the. . . between MMP's and serine proteinases during tissue breakdown, 1) cathepsin G can activate MMP-8; 2) the serine proteinase Human Leukocyte **Elastase** (HLE) can inactivate TIMP's, the major endogenous Tissue Inhibitors of Matrix Metalloproteinases, 3) MMP-8 and MMP-9 can activate .alpha..sub.1 -Proteinase Inhibitor (.alpha..sub.1 -PI), the major endogenous inhibitor of human leukocyte **elastase**, (S. K. Mallya, et al., Annuals of the New York Academy of Science, 1994, 732:303-314) and 4) tumor-associated-trypsin-2 can efficiently. . .

SUMM U.S. Pat. No. 5,773,430 to Simon et al. describes using hydrophobic tetracyclines to inhibit excess leukocyte **elastase** serine proteinase activity in a biological system.

DETD . . . marked inflammation in the periodontal tissues and induces elevated levels of tissue-destructive matrix metalloproteinases (MMPs) and serine proteinases such as **elastase** in the gingiva leading to severe alveolar bone resorption and bone loss around the affected teeth, all within the 7-day. . . of these destructive pathways, often
reducing these levels in the endotoxin-injected tissues to the normal levels of collagenases, gelatinases and **elastase** seen in the saline-injected (control) tissues.

DETD . . . synergistically inhibits the activities of pure human cell bound MT.sub.1 -MMP and extracellular collagenases, gelatinases (extracellular MMP's) as well as **elastase** (serine proteinase).

DETD . . . on day 7. As described above, the gingival tissues were dissected, extracted and the partially-purified extracts analyzed for neutral proteinase (**elastase** and matrix metalloproteinase) activities, and both tooth mobility and alveolar bone loss were assessed.

DETD **elastase** activity was measured spectrophotometrically using a synthetic peptide substrate specific for neutrophil (inflammatory cell) **elastase**.

DETD . . . 1997, 36:310-317). It is noteworthy that all of these assays demonstrated synergistic inhibition of the activities of these MMP-proteinases and **elastase** as well as the down-regulation of the level of these enzymes due to combination (CMT plus bisphosphonate) therapy.

ACCESSION NUMBER: 1999:160006 USPATFULL
TITLE: Combination of bisphosphonate and tetracycline
INVENTOR(S): Ramamurthy, Nungavarm S., Smithtown, NY, United States
Golub, Lorne M., Smithtown, NY, United States
Sorsa, Timo A., Helsinki, Finland
Teronen, Olli P., Helsinki, Finland
Salo, Tuula A., Oulu, Finland
PATENT ASSIGNEE(S): The Research Foundation of State University of New York, Albany, NY, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5998390	19991207	
APPLICATION INFO.:	US 1998-161804	19980928	(9)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Krass, Frederick
LEGAL REPRESENTATIVE: Hoffmann & Baron, LLP
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EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 8 Drawing Page(s)
LINE COUNT: 862
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L6 ANSWER 3 OF 4 USPATFULL
CLM What is claimed is:

1. A method for inhibiting the production and activity of proteinases in a biological system in which such inhibition is desired, comprising administering thereto a proteinase inhibiting amount of a composition comprising a synergistic combination of a tetracycline and a bisphosphonate.

2. The method of claim 1 wherein the biological system is mammalian.

3. The method of claim 1 wherein the composition further comprises a pharmaceutical preparation or carrier.

4. The method of claim 1 wherein the excess proteinase production and activity are associated with connective tissue and/or basement membrane degradation.

5. The method of claim 1 wherein the proteinase is matrix metalloproteinase (MMP), an MMP-like enzyme or a serine proteinase or a combination thereof.

6. The method of claim 4 wherein the tissue degradation is associated with tissue invasion and metastasis by malignant cells, osteoporotic bone loss, bone resorption, cartilage destruction, angiogenesis or destruction of soft tissues.

7. The method of claim 1 wherein the tetracycline, which is non-antimicrobial, and the bisphosphonate are present in synergistic

amounts for inhibiting the production and/or activity of excess proteinase.

8. The method of claim 1 wherein the tetracycline is CMT-1,CMT-3, CMT-8, doxycycline, minocycline, lymecycline or combinations thereof, and the bisphosphonate is alendronate, clodronate (clodrinate), etidronate, pamidronate, medronate, nedrinate, tiludronate, zolendronate or combinations thereof.

demonstrated synergistic inhibition of the activities of these MMP-proteinases and **elastase** as well as the down-regulation of the level of these enzymes due to combination (CMT plus bisphosphonate) therapy.

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